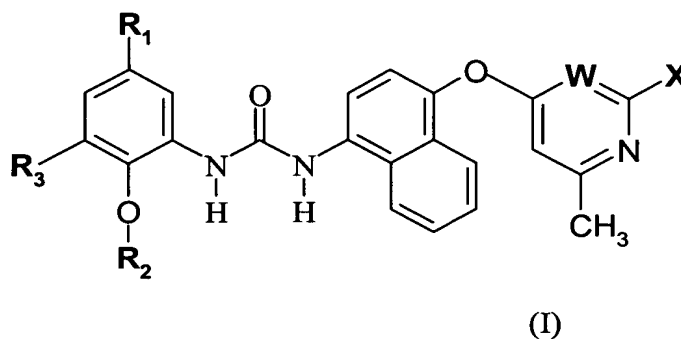


**What is Claimed is:**

1. A compound of the formula (I):



wherein

**R<sub>1</sub>** is -CF<sub>3</sub>, -CH(CH<sub>3</sub>)(CF<sub>3</sub>), -CH(CF<sub>3</sub>)<sub>2</sub>, -OCF<sub>3</sub>, -CF<sub>2</sub>CF<sub>3</sub>;

**R<sub>2</sub>** is C<sub>1-5</sub> alkyl;

**R<sub>3</sub>** is attached at the 3- or 4-position on the phenyl ring and is hydrogen, -NH<sub>2</sub> or **R<sub>4</sub>**-S(O)<sub>2</sub>-NH- wherein **R<sub>4</sub>** is chosen from C<sub>1-5</sub> alkyl or carbocycle;

**W** is CH or an N atom;

**X** is chosen from

C<sub>1-5</sub> alkyl or C<sub>1-5</sub> alkoxy each optionally substituted by mono- or di-C<sub>1-3</sub> alkyl amino, morpholinyl, piperazinyl, pyrrolidinyl, triazolyl, imidazolyl or piperadinyl each ring being further optionally substituted with C<sub>1-3</sub> alkyl;

or **X** is -N(**R<sup>a</sup>**)<sub>2</sub> wherein **R<sup>a</sup>** is independently chosen from hydrogen, C<sub>1-5</sub> alkyl, aryl, arylC<sub>1-3</sub> alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkyl C<sub>1-3</sub> alkyl, C<sub>1-5</sub>alkoxyC<sub>1-5</sub>alkyl and heterocyclyl C<sub>1-3</sub> alkyl wherein the heterocyclyl is chosen from tetrahydrofuran,

pyrrolidinyl and morpholinyl, each  $R^a$  where possible is optionally substituted by one to two C1-5 alkyl, C1-5 alkoxy, hydroxy, halogen or amino optionally mono- or di-substituted by C1-3 alkyl;

5 or the pharmaceutically acceptable acids, esters, salts or isomers thereof.

2. The compound according to claim 1 wherein:

10  $R_1$  is  $-CF_3$ ,  $-CH(CH_3)(CF_3)$ ,  $-CH(CF_3)_2$ ,  $-OCF_3$  or  $-CF_2CF_3$ ;

$R_2$  is  $C_{1-3}$  alkyl;

$W$  is an N atom;

15

$X$  is chosen from

C1-5 alkyl or C1-5 alkoxy each optionally substituted by mono- or di-C1-3 alkyl amino, morpholinyl, piperazinyl, pyrrolidinyl, triazolyl, imidazolyl or piperadinyl each ring being further optionally substituted with C1-3 alkyl;

20

or  $X$  is  $-N(R^a)_2$  wherein  $R^a$  is independently chosen from hydrogen, C1-5 alkyl, phenylC1-3 alkyl, C3-6cycloalkyl, C3-6cycloalkyl C1-3 alkyl, C1-3alkoxyC1-3alkyl and heterocyclyl C1-3 alkyl wherein the heterocyclyl is chosen from tetrahydrofuran, pyrrolidinyl and morpholinyl, each  $R^a$  where possible is optionally substituted by one to  
25 two C1-3 alkyl, C1-3 alkoxy, hydroxy, halogen or amino optionally mono- or di-substituted by C1-2 alkyl.

3. The compound according to claim 2 wherein:

30  $R_1$  is  $-CF_3$ ,  $-CH(CH_3)(CF_3)$ ,  $-CH(CF_3)_2$  or  $-CF_2CF_3$ ;

$R_2$  is  $C_{1-2}$  alkyl.

4. The compound according to claim 3 wherein:

5  $R_1$  is  $-CF_3$ ;

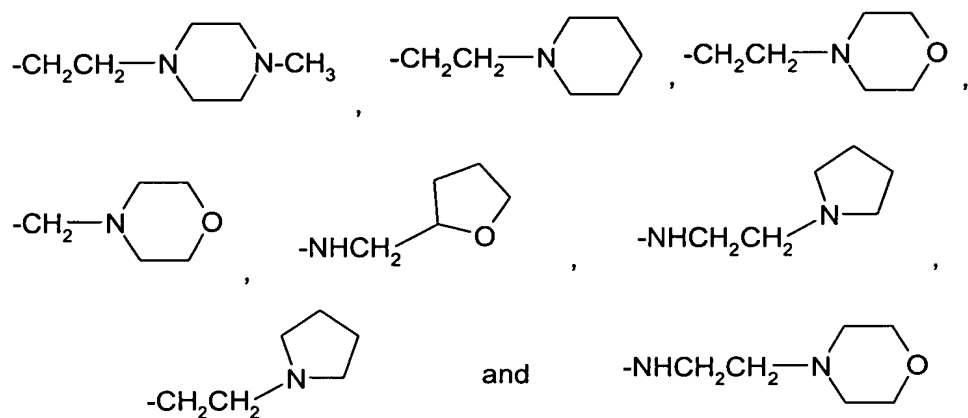
$R_2$  is  $-CH_3$ .

10 5. The compound according to claim 4 wherein:

$X$  is chosen from

15  $NH_2$ ,  $NH(CH_3)$ ,  $-NHCH_2CH_2N(CH_3)_2$ ,  $-NHCH_2CH_2-O-CH_3$ ,  $-CH_2-N(CH_3)_2$ ,  $-CH_2CH_2-$   
 $N(CH_3)_2$ ,  $-CH_2CH_2CH_2-N(CH_3)_2$ ,  $-CH_2CH_2CH_2CH_2-N(CH_3)_2$ ,  $-CH_2-NH(CH_3)$ ,  
 $-CH_2CH_2-NH(CH_3)$ ,  $-CH_2CH_2CH_2-NH(CH_3)$ ,  $-CH_2CH_2CH_2CH_2-NH(CH_3)$ ,  
 $-O-CH_2-N(CH_3)_2$ ,  $-O-CH_2CH_2-N(CH_3)_2$ ,  $-O-CH_2CH_2CH_2-N(CH_3)_2$ ,  
 $-O-CH_2CH_2CH_2CH_2-N(CH_3)_2$ ,  $-OCH_2-NH(CH_3)$ ,  $-O-CH_2CH_2-NH(CH_3)$ ,  
 $-O-CH_2CH_2CH_2-NH(CH_3)$ ,  $-O-CH_2CH_2CH_2CH_2-NH(CH_3)$ ,

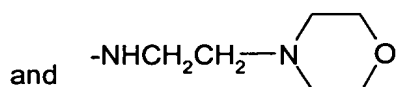
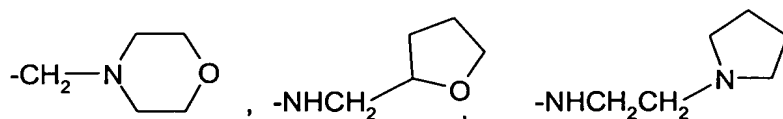
20



6. The compound according to claim 5 wherein:

X is chosen from

- 5  $\text{NH}_2$ ,  $\text{NH}(\text{CH}_3)$ ,  $-\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ ,  $-\text{NHCH}_2\text{CH}_2-\text{O}-\text{CH}_3$ ,  $-\text{CH}_2-\text{N}(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2$ ,  $-\text{CH}_2-\text{NH}(\text{CH}_3)$ ,  $-\text{CH}_2\text{CH}_2-\text{NH}(\text{CH}_3)$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}(\text{CH}_3)$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}(\text{CH}_3)$ ,  $-\text{O}-\text{CH}_2-\text{N}(\text{CH}_3)_2$ ,  $-\text{O}-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2$ ,  $-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2$ ,  $-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2$ ,  $-\text{OCH}_2-\text{NH}(\text{CH}_3)$ ,  $-\text{O}-\text{CH}_2\text{CH}_2-\text{NH}(\text{CH}_3)$ ,  $-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}(\text{CH}_3)$ ,  $-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}(\text{CH}_3)$ ,
- 10  $-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}(\text{CH}_3)$ ,  $-\text{O}-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}(\text{CH}_3)$ ,



- 15 7. A compound chosen from:

1-[4-(2-Amino-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(6-methyl-2-morpholin-4-ylmethyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-urea;
1-{4-[2-(2-Dimethylamino-ethylamino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-{4-[2-(2-Methoxy-ethylamino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;

1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-(4-{6-methyl-2-[(tetrahydro-furan-2-ylmethyl)-amino]-pyrimidin-4-yloxy}-naphthalen-1-yl)-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{4-[6-methyl-2-(2-pyrrolidin-1-yl-ethylamino)-pyrimidin-4-yloxy]-naphthalen-1-yl}-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{4-[6-methyl-2-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yloxy]-naphthalen-1-yl}-urea;
1-[4-(2-Cyclopropylamino-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-{4-[2-(2-Methoxy-1-methyl-ethylamino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-{4-[2-(2,3-Dihydroxy-propylamino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-[4-(2,6-Dimethyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-[4-(2-Methoxy-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea and
N-(3-{3-[4-(2,6-Dimethyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-ureido}-2-methoxy-5-trifluoromethyl-phenyl)-methanesulfonamide

or the pharmaceutically acceptable acids, esters, salts or isomers thereof.

5

8. A compound chosen from:

1-[4-(2-Ethylamino-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-{4-[2-(Cyclopropylmethyl-amino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-[4-(2-Isopropylamino-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-[4-(2-Amino-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-[2-methoxy-5-(2,2,2-trifluoro-1-methyl-ethyl)-phenyl]-urea;
1-[4-(2-Amino-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-[2-methoxy-5-(2,2,2-trifluoro-1-trifluoromethyl-ethyl)-phenyl]-urea;
1-[4-(2-Amino-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-[2-methoxy-5-(2,2,2-trifluoro-ethyl)-phenyl]-urea;
1-[4-(2-Methylamino-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-trifluoromethoxy-phenyl)-urea;
1-(2-Methoxy-5-trifluoromethoxy-phenyl)-3-[4-(6-methyl-2-ethylamino-pyrimidin-4-yloxy)-naphthalen-1-yl]-urea;
1-{4-[2-(2-Dimethylamino-ethylamino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethoxy-phenyl)-urea;
1-(2-Methoxy-5-trifluoromethoxy-phenyl)-3-{4-[6-methyl-2-(2-pyrrolidin-1-yl-ethylamino)-pyrimidin-4-yloxy]-naphthalen-1-yl}-urea;
1-{4-[2-(2-Methoxy-ethylamino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethoxy-phenyl)-urea;
1-(2-Methoxy-5-trifluoromethoxy-phenyl)-3-[4-(6-methyl-2-morpholin-4-ylmethyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-urea;
1-(2-Methoxy-5-trifluoromethoxy-phenyl)-3-{4-[6-methyl-2-(4-methyl-piperazin-1-ylmethyl)-pyrimidin-4-yloxy]-naphthalen-1-yl}-urea;

1-(2-Methoxy-5-trifluoromethoxy-phenyl)-3-[4-(6-methyl-2-pyrrolidin-1-ylmethyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-urea;
1-[4-(2-Dimethylaminomethyl-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-trifluoromethoxy-phenyl)-urea;
1-{4-[2-(2-Imidazol-1-yl-ethoxy)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethoxy-phenyl)-urea;
1-[2-Methoxy-5-(2,2,2-trifluoro-ethyl)-phenyl]-3-{4-[6-methyl-2-(1-methyl-piperidin-4-ylmethoxy)-pyrimidin-4-yloxy]-naphthalen-1-yl}-urea;
1-{4-[2-(3-Dimethylamino-propylamino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-[2-methoxy-5-(2,2,2-trifluoro-ethyl)-phenyl]-urea;
1-[2-Methoxy-5-(2,2,2-trifluoro-ethyl)-phenyl]-3-{4-[6-methyl-2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yloxy]-naphthalen-1-yl}-urea;
1-(2-Methoxy-5-trifluoromethoxy-phenyl)-3-{4-[6-methyl-2-(3-morpholin-4-yl-propylamino)-pyrimidin-4-yloxy]-naphthalen-1-yl}-urea;
1-[4-(2-Amino-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-pentafluoroethyl-phenyl)-urea;
1-{4-[2-(Cyclopropylmethyl-amino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-{4-[2-(2-Dimethylamino-ethylamino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-[2-methoxy-5-(2,2,2-trifluoro-1-trifluoromethyl-ethyl)-phenyl]-urea;
1-[2-Methoxy-5-(2,2,2-trifluoro-1-trifluoromethyl-ethyl)-phenyl]-3-[4-(6-methyl-2-morpholin-4-ylmethyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-urea;

1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{4-[6-methyl-2-(4-methyl-piperazin-1-ylmethyl)-pyrimidin-4-yloxy]-naphthalen-1-yl}-urea; and
1-[4-(2-Dimethylaminomethyl-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea

or the pharmaceutically acceptable acids, esters, salts or isomers thereof.

9. A compound chosen from

1-[4-(2-Amino-6-methyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(6-methyl-2-methylamino-pyrimidin-4-yloxy)-naphthalen-1-yl]-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-[4-(6-methyl-2-morpholin-4-ylmethyl-pyrimidin-4-yloxy)-naphthalen-1-yl]-urea;
1-{4-[2-(2-Dimethylamino-ethylamino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-{4-[2-(2-Methoxy-ethylamino)-6-methyl-pyrimidin-4-yloxy]-naphthalen-1-yl}-3-(2-methoxy-5-trifluoromethyl-phenyl)-urea;
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{4-[6-methyl-2-(2-pyrrolidin-1-yl-ethylamino)-pyrimidin-4-yloxy]-naphthalen-1-yl}-urea; and
1-(2-Methoxy-5-trifluoromethyl-phenyl)-3-{4-[6-methyl-2-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yloxy]-naphthalen-1-yl}-urea

5 or the pharmaceutically acceptable acids, esters, salts or isomers thereof.



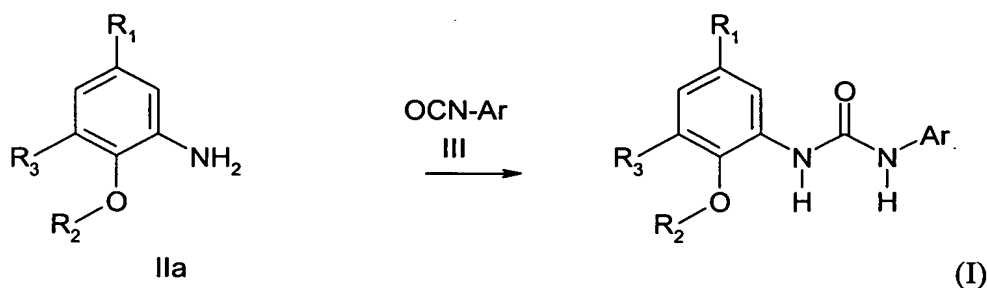
10. A pharmaceutical composition containing a pharmaceutically effective amount of a compound according to claim 1 and one or more pharmaceutically acceptable carriers and/or adjuvants.

5 11. A method of treating a cytokine mediated disease or condition comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound according to claim 1.

12. The method according to claim 11 wherein cytokine mediated disease or condition is  
10 selected from rheumatoid arthritis, inflammatory bowel disease, septic shock, osteoarthritis, Crohn's disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, graft versus host disease, systemic lupus erythematosus, restenosis following percutaneous transluminal coronary angioplasty, diabetes, toxic shock syndrome, Alzheimer's disease, acute and chronic pain, contact dermatitis,  
15 atherosclerosis, traumatic arthritis, glomerulonephritis, reperfusion injury, sepsis, bone resorption diseases, chronic obstructive pulmonary disease, congestive heart failure, asthma, stroke, myocardial infarction, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, dermatoses with acute inflammatory components, acute purulent meningitis, necrotizing enterocolitis and syndromes  
20 associated with hemodialysis, leukopheresis and granulocyte transfusion.

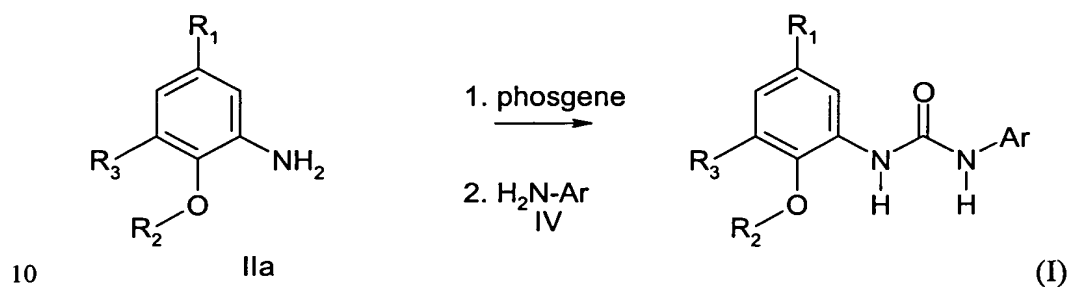
13. A process for preparing compounds of the formula (I) according to claim 1, wherein:

a) an arylamine of formula IIa and an arylisocyanate of formula III is dissolved in a non-  
25 protic, anhydrous solvent chosen from THF, ether, toluene, dioxane or ethyl acetate, between 0 - 45° C, for 2-24 h, and subsequently isolating the product of formula I or precursors thereof;



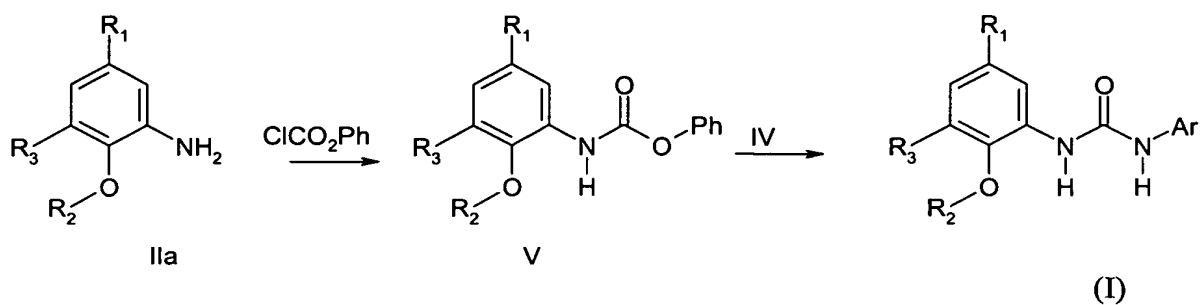
or

- b)** dissolving an arylamine of formula **IIa** in a halogenated solvent, diluting the mixture with aqueous alkali and combining with phosgene to provide the corresponding isocyanate, mixing the isocyanate and arylamine **IV** in a non-protic, anhydrous solvent selected from THF, ether, toluene, dioxane, dichloromethane or ethyl acetate at between about 0 - 45° C and subsequently isolating to provide the product of formula **I** or precursors thereof;



or

- c)** dissolving an arylamine of formula **IIa** in a suitable halogenated solvent optionally adding a suitable base followed by an alkyl or aryl chloroformate between 0 - 85° C, for 2 - 24 h, providing carbamate **V**, mixing carbamate **V** and arylamine **IV** in a non-protic, anhydrous solvent selected from THF, ether, toluene, dioxane, dichloromethane or ethyl acetate, between 0 - 110 °C, for 2 - 24 h, subsequently isolating to provide the product of formula **I** or precursors thereof;



or

- 5 d) dissolving an aromatic carboxylic acid in a non-protic solvent and an inorganic base, cooling the mixture is to  $-30-0^\circ\text{C}$ , adding an alkyl chloroformate at  $0^\circ\text{C}$  for 1-3 hours, adding sodium azide in water diluted with toluene followed by heating for 1-4 hours, cooling to room temperature to give isocyanate (Va), reacting isocyanate (Va) with amine (IV), subsequently isolating to give product of formula I or precursors
- 10 thereof;

